Rationale and Methods for the Treatment of Early Essential Hypertension*

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GIVEN a reasonable amount of knowledge and common sense the treatment for uncomplicated hypertension today can be made relatively effective, simple and safe. This recent advance necessitates a critical review of old attitudes and opinions, for it is now possible to reduce blood pressure in many mild and moderate cases with little or no discomfort to the patient. Has therapy been perfected? No, far from it. But it is now possible to achieve better control more easily in a higher precentage of patients than was possible in the past.

THE QUESTION OF EARLY TREATMENT

Should this development alter present attitudes toward the management of the early, mild cases? Until now general policy has been to treat the uncomplicated, early cases symptomatically and "conservatively," reserving antihypertensive therapy for patients with more advanced disease. This nihilistic approach was justified when we could offer only drastic surgery, stringent diets or "tricky" hypotensive drugs. But is it justified today?

Therapeutic philosophy in many diseases carries with it a tradition from the past. In the case of hypertension this tradition from older times is one of therapeutic nihilism. The administration of the unsatisfactory therapeutic agents available 20 years ago was rightly looked upon as bordering on charlatanism. Our elders' attitude can be sensed in the very name "essential" hypertension suggesting that the elevated blood pressure was a compensation and was necessary in some way for the patient's welfare.

Rightly or wrongly, a negativistic attitude persists in many quarters today. These critics point out that a controlled study over a period of sufficient time to determine the value of blood pressure reduction has not been carried out. But, such a study would involve a collaborative effort of several hospitals and a time period of five to ten years or more. Such a study is, in fact, in progress in the Veterans Administration, but it will be many years before definitive proof becomes available that antihypertensive agents prolong life or prevent complications in the milder cases. Are we justified in doing nothing about early hypertension while awaiting for final proof? Let us examine the argument from another aspect.

Antihypertensive therapy is based on a rationale here described. It is granted that we do not know, and hence, cannot remove the ultimate cause of essential hypertension. Therefore, we cannot cure. But to an increasing degree from year to year as more effective agents are developed we can control the hypertension. If the level of blood pressure can be controlled at normotensive or nearly normotensive levels, then the organic progression, such as cardiac hypertrophy and vascular degenerative changes, will not occur.

If this argument is valid it should be possible to demonstrate that elevation of blood pressure in the arterial tree, *per se*, produces the organic damage. In brief, we must ask the question

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whether the cardiac, renal and vascular damage in hypertension is due to the hydraulic effect of the elevated pressure, or is associated rather with some unknown toxic factor acting to damage the walls of arteries and arterioles.

ARTERIOLOSCLEROSIS IN HYPERTENSION

Part of the answer to this question lies in determining whether the characteristic arteriolar lesions precede or follow the hypertension. In the past it was thought that thickening of the internal layer of the arterioles was a primary process and that the resultant narrowing produced the hypertension. This impression was gained from autopsy examination in patients dying in the advanced stages of hypertensive disorders. However, it is now known that although the proliferation of the intima is a constant finding in cases of long standing or rapidly advancing hypertension it is not seen early in the course of benign essential hypertension. The absence of organic arteriolar changes in the early cases has been shown in renal biopsies by Castleman and Smithwick[1] and in muscle biopsies by Evelyn[2]. In early hypertension there is no observable pathological change in the arterioles. There is rather a functional constriction, a narrowing due to spasm as can be seen in the fundi, but not intimal proliferation and fibrosis. Byrom has shown in the meningeal arterioles of hypertensive rats that the spasm is relieved when the blood pressure is reduced[3].

If the organic arteriolar changes follow rather than precede the hypertension it is possible that they may be produced by the hypertension or the long continued spasm associated therewith. A clue to this question was supplied by Wilson and Byrom in their experiments on the hypertension produced by constricting a renal artery in the rat[4]. Distal to the clamp there was not only a decrease in blood flow but also in blood pressure. Because of the constriction a severe hypertension developed in the animal's body, except, in the kidney protected by the arterial constriction.

It was significant that the animals who died of malignant hypertension exhibited at autopsy arteriolosclerotic and necrotic lesions in certain visceral organs including the kidney opposite to the clamp, but not in the kidney on the same side as the clamp. Obviously, if there were any toxic substance circulating in the blood which produced the organic arteriolar changes it could affect both kidneys since the blood supply was only diminished and was not cut off completely. However, the pressure distal to the clamp was sharply reduced due to the arterial coarctation. Thus, it seems reasonable to conclude that the arterioles showing organic degenerative changes did so because they were subjected to a high head of blood pressure, whereas in the area where the pressure was low the arteriolar changes could not develop.

These observations in the rat have been confirmed in man. Blahd reported a case of malignant hypertension which at autopsy was found to be associated with a thrombosis of one main branch of a renal artery[5]. Sufficient blood supply was received from other branches so that infarction did not occur. Typical arteriolosclerotic and arteriolonecrotic lesions were present in both kidneys *except* in the area supplied by the thrombosed artery. Brust and Ferris presented a series of patients with hypertension due to unilateral renal disease[6]. They emphasized the fact that in the patients with "Goldblatt kidney" degenerative arteriolar lesions were limited to the areas exposed to high blood pressures and were not found in the areas distal to coarcted arteries. Thus, in man also, arteriolosclerosis does not seem to be a primary process but seems rather to be a reaction to an abnormal elevation of arterial pressure.

ATHEROSCLEROSIS IN HYPERTENSION

However, many hypertensive patients die or are disabled not from arteriolosclerosis but by atherosclerosis of larger arteries, coronary and cerebral. What can be said about the cause and effect relationship between hypertension and atherosclerosis of large vessels? First, it should be pointed out that there is a higher incidence of coronary and cerebral atherosclerosis in the hypertensive than in the normotensive population. The incidence of cerebral thrombosis is so obviously higher in hypertensives that it needs no further comment. In regard to coronary atherosclerosis, studies by Goldstein and his coworkers[7] showed that the incidence of myocardial infarction was four to five times higher in hypertensives than in normotensive males and 21 times higher in hypertensive than in normotensive females. In the carefully controlled Framingham Study on coronary atherosclerosis, hypertension was found to have a high

statistical correlation. Thus, there is good evidence that coronary as well as cerebral atherosclerosis is much more prevelant in hypertensive than in normotensive individuals.

Something is present in hypertensives which accelerates the atherosclerotic process. Is the acceleration also due to the elevated pressure, *per se,* or to some other mysterious factor, some unknown circulating noxious agent associated with the hypertensive process? In this regard it is pertinent to discuss the autopsy observations made in patients who had longstanding pulmonary hypertension due to certain forms of congenital heart disease. These were patients who survived to young adult life with conditions such as patent ductus arteriosus with right to left shunt or with large intraventricular septal defects or a single common ventricle. In these patients the pulmonary arterial pressure was markedly elevated for many years approaching the systemic pressure. At autopsy, extensive atherosclerosis usually was found not of systemic arteries, but of the pulmonary arteries.

It seems highly significant that the atherosclerosis occurs so frequently in areas subjected to abnormally high pressure and avoids areas of low pressure, sparing the pulmonary arteries in systemic hypertension and the systemic arteries in pulmonary hypertension. Not long ago we saw a young man at autopsy who died following repair of a coarctation of the aorta. He was hypertensive only in the area above the coarctation. That portion of the aorta subjected to high pressure was covered with early placques, whereas below the coarctation in the area of lower pressure not a single placque could be found. These various observations have impressed me that high pressure within a vessel is one of the factors favoring the deposition of lipids in the intima of arteries. However, I do not wish to imply that hypertension causes atherosclerosis, but rather that the hydraulic effect of a high pressure within an artery accelerates the atherosclerotic process.

OTHER ORGANIC COMPLICATIONS

Another major cause of death and disability in hypertension is congestive heart failure. Few can deny that for the left ventricle to maintain a normal output in the face of an increased peripheral resistance it must hypertrophy and dilate. This process of compensation has its limits, however, beyond which the output begins to fall off and failure develops. It also has been amply demonstrated in such patients that when the systemic pressure is reduced by anti-hypertensive agents the failure is ameliorated and the dilatation if not the hypertrophy may regress.

It also is reasonable to believe that the complication of cerebrovascular hemorrhage, which is so common in hypertensive as compared to normotensive individuals, may well be associated with the presence of high pressure within the cerebral arterial system.

Thus, if one looks at the evidence available today and attempts to form an unbiased judgement as to whether hypertension is merely a meaningless symptom or the principle cause of the disabling and fatal organic complications, he will find far more evidence to indicate the latter than the former.

BLOOD PRESSURE AND LONGEVITY

If you believe that hypertension is a meaningless symptom you are led straight to therapeutic nihilism. But, if you say that the high pressure existing within the arterial tree is the major factor in producing organic cardiovascular damage you will be led to treatment aimed at reduction of the elevated levels. In addition, you will treat early, before the damage has occurred. We cannot expect to be very successful in dissolving atherosclerotic placques or in restoring scarred arterioles; yet many physicians will treat only these advanced cases, choosing to be more "conservative" with the younger, benign essential hypertensives. They argue that the benign cases live out a normal or nearly normal life span anyway. So why bother?

But do they? Perera found in his studies of hypertension that when the disease begins in the thirties the life span from onset to death averages about 20 years[8]. In 1940 the life insurance companies pooled their data to determine the relationship between blood pressure levels and life expectancy[9]. Their figures were based on the follow-up of hundreds of thousands of insured individuals. They demonstrated a smooth curve relationship between the level of blood pressure and longevity, the higher the pressure the poorer the outlook. Also worthy of note is that the values, particularly in regard to systolic pressure, pay no attention to

the normal range. For example, the average individual with a systolic of 115 can look forward to a longer life span than the one with a pressure of 135.

The studies by the life insurance companies throw serious doubt on the argument that hypertension is a benign process. It is, rather, the exceptional cases, usually females with labile blood pressures, that stand out in the physician's mind. These labile, middle aged, females impress us overly much and should be differentiated from males and from all young adult hypertensives with more persistent elevations of diastolic pressure. The latter, in my opinion, should be treated before they develop irreversible organic changes, when they are still called early and "benign."

METHODS OF TREATMENT

In general, the earlier the hypertension the easier it is to control the blood pressure. The treatment of severe hypertension is a job for the specialist who has had considerable experience with such problems. Therefore, the subsequent discussion will be devoted to the management of mild, moderate and early hypertension, since it is here that general practitioners and internists, as opposed to the hypertensive specialist, can make their most valuable contribution.

A great number of agents acting at many different sites in the body have been found to have antihypertensive effects. Some of these are not practical for general use. The important agents for the present purposes are chlorothiazide (Diuril) which acts on the kidney increasing the excretion of salt; hydralazine (Apresoline) which seems to have several sites of action, a peripheral action directly on arterioles, a central action in the higher autonomic centers and possibly also a very mild adrenergic blocking action; Rauwolfia, including its active alkaloid, reserpine, which seems to act in the area of the hypothalamus and which also antagonizes serotonin; and the ganglionic blocking agents which inhibit the transmission of impulses throughout all antonomic ganglia.

CHLOROTHIAZIDE (DIURIL)

Chlorothiazide seems to represent a most valuable addition to the treatment of hypertensive patients. It is easy to administer and seems to be relatively free of discomforting side effects. While only moderately effective as an antihypertensive agent in its own right, it demonstrates a remarkable ability to enhance the antihypertensive activity of other agents, particularly the ganglionic blocking drugs and hydralazine.

Chlorothiazide produces considerable salt depletion even in nonedematous individuals[10]. In balance studies on a nonedematous hypertensive patient the intake of sodium and chloride was maintained at 70 mEq per day. Following chlorothiazide (500 mg. three times daily) sodium and chloride excretion increased markedly and potassium to a lesser extent. The excess loss of chloride and sodium (representing depletion of body stores) averaged about 350 mEq. during the first 48 hours. This was accompanied by a decrease in blood pressure. Despite continuation of chlorothiazide, the excess salt and potassium excretion tapered off after the first 48 hours and after five days came into balance with the intake.

Accompanying the increased excretion of electrolyte, there was a depletion of extracellular fluid space as reflected in a decrease in sodium, sulfate, or SCN spaces, plasma volume, body weight and an increase in the hematocrit. As yet, unpublished observations from our laboratory suggest that the antihypertensive effect of chlorothiazide is dependent upon the plasma volume depletion and can be abolished by giving 500 ml. of Dextran. Serum concentrations of sodium and chloride fell only slightly, if at all, except in unusual patients with severe renal or cardiac damage. Electrocardiographic changes suggesting electrolyte depletion have not been seen except in the unusual cases mentioned. Serum potassium levels, however, fell quite frequently. This has become troublesome in patients with congestive heart failure who are already in a potassium depleted state[11]. Unfortunately, relatively small degrees of K loss will markedly reduce the threshold of sensitivity to digitalis. Therefore, anorexia, nausea and arrhythmias due to digitalis, plus slight hypokalemia have been the most common side effects of chlorothiazide[12].

The optimal dose of chlorothiazide in hypertension is 500 mg. twice daily. This amount is usually required to maintain the antihypertensive effect; it must be given daily and not intermittently as in the treatment of edematous states. There is little advantage and somewhat more danger in giving more than this amount. We have made a point of ad-

ministering the first dose on arising and the second on retiring. Since patients eat their main meal at night the salt losing effects of the morning dose will be dissipated by evening permitting the patient to absorb and distribute the ingested potassium prior to the last dose at bedtime. It has not been necessary to use potassium supplements except in the patients taking digitalis. In most hypertensive cardiacs, digitalis can be discontinued after the blood pressure has been reduced and the edema cleared.

The patient achieves an enhanced antihypertensive effect from chlorothiazide if he observes at least moderate salt restriction in his diet. When the salt intake was raised from four to a range of 11 to 25 grams per day, the blood pressure rose somewhat despite continuation of chlorothiazide and only fell again when the salt intake was reduced. This provides additional evidence to indicate that the antihypertensive effect of chlorothiazide is associated with its salt depleting action. The antihypertensive effect of the drug can be improved by restricting, at least moderately, the salt content of the diet. This does not imply rigid restriction which most patients would not observe anyway, but, rather, a moderate restriction such as avoidance of heavily salted foods and elimination of the salt shaker at the table.

The reduction of mean blood pressure on chlorothiazide alone in hospitalized hypertensive patients averaged 16 per cent. However, when chlorothiazide was added to other antihypertensive agents the reduction from pretreatment levels approached 30 per cent.

Chlorothiazide was added to the treatment regimen of 73 ambulatory hypertensive patients[11]. These had been carefully followed, most of them taking their blood pressures at home for one month to three years prior to chlorothiazide therapy. A variety of treatments had been used: ganglionic blocking agents with or without reserpine and/or hydralazine, veratrum alone or in combination and reserpine alone or with hydralazine. Most of these were patients with moderately severe hypertension. Only one had malignant hypertension. A few had quite mild hypertension. Immediately before chlorothiazide, the reduction of blood pressure for the entire group averaged 11 per cent from pretreatment levels. Following the addition of chlorothiazide, the reduction averaged 27 per cent. This additional reduction occurred despite the fact that the ganglionic blocking agents were discontinued in 19 of the 32 cases taking these drugs and their dosages reduced in the remainder. Usually, however, hydralazine was continued or substituted.

It is important to bear in mind the enhancement of the activity of the ganglionic blocking agents by chlorothiazide. It was essential to reduce the dosage of blocking agent to half the prior effective dose when chlorothiazide was instituted. Otherwise, the patients may develop severe postural hypotension and collapse. After reducing the dosage of the blocking agent in half, it was possible to raise or lower the dosage as indicated after the chlorothiazide had been instituted in order to obtain optimal results. I believe that home blood pressure recordings are essential in using this potent combination. By the same token, patients who have had surgical sympathectomy for hypertension in the past were unusually responsive to chlorothiazide.

HYDRALAZINE (APRESOLINE)

The discovery of chlorothiazide has returned hydralazine (Apresoline) to prominence since the two make an effective combination in many patients even though small, and hence, safe doses of hydralazine can be used. The combination is well tolerated.

The acute side effects of hydralazine are uncomfortable at times, but not serious. The drug produces an increase in cardiac output at the same time that it reduces blood pressures. This effect on the heart which is most pronounced in the first few days of treatment produces the acute effects of palpitation and dyspnea on slight exertion. Angina if present may be aggravated. Hydralazine produces arteriolar dilitation, including the cerebral vessels, which can result in severe headache. This effect also is seen only in the early stages of treatment. These acute side effects rarely occur if chlorothiazide is given concomittantly with the hydralazine and if the hydralazine is instituted gradually and in low dosage. One can usually begin with a dose of 25 mg. three times daily and increase gradually, if necessary, to a level of 50 mg. three times daily. Thus, if two precautions are observed: first, to use hydralazine not alone but in combination with chlorothiazide and second, to begin with a

small dose and gradually increase, the acute side effects seldom need occur.

The chronic side effects which are potentially quite serious consist of hypersensitivity reactions, the most important being a syndrome resembling disseminated lupus with L. E. cells demonstrable in the peripheral blood. This reaction characteristically occurs in patients taking high dosages for long periods of time. It rarely if ever occurs when the dosage is kept below 200 mg. per day. For this reason the drug can be considered to be quite safe if the daily dosage does not exceed 150 mg. per day. Fortunately, this level of dosage, and even smaller in many early hypertensives, has been quite effective in controlling blood pressure in the less severe cases when combined with chlorothiazide. In general, the less hydralazine required the better.

RAUWOLFIA AND RESERPINE

Rauwolfia and its most active alkaloid, reserpine, have been so widely used by almost all physicians for the treatment of hypertension that they require little comment. Ordinarily, this is not as effective an antihypertensive agent as the two just discussed. Its advantages are a simple dosage schedule (we use 0.5 mg. of reserpine twice daily for two weeks, followed by a maintainence dose of 0.1 to 0.25 mg. daily). Some patients are unable to endure taking the drug because it produces a disturbing lethargy, loss of drive and vague depression. Others are quite happy with the emotional change it produces. Some patients are troubled with nasal stuffiness, particularly at night, which may be difficult to control, although, antihistaminics sometimes are helpful as is reduction of maintainance dosage. The drug apparently produces hyperemia of the nasal mucosa which can lead to prolonged and severe epistaxis in occasional patients.

The most serious side effect is a severe depression coming on insidiously usually after months of therapy. Some suicides have occurred as a result of this depression. The higher the maintainence dose the more likely are such depressions, and for this reason, the maintenance dose should be kept as low as possible, that is about 0.1 to 0.25 mg. reserpine daily. It is interesting that the more intellectual and sensitive individuals are most prone to develop these serious mental depressions following Rauwolfia. I have seen it develop frequently in physicians, teachers and clergymen and have almost never seen it in the clinic type patient.

At any rate, the Rauwolfia alkaloids are not the benign tranquilizing agents in all patients that they are reported to be. They are, however, useful in many patients with mild and moderate hypertension providing the physician watches his patient's reactions with alertness and sympathy and keeps his maintainence dosages low.

GANGLIONIC BLOCKING AGENTS

Chlorothiazide also has influenced favorably treatment with the ganglionic blocking agents, but at the same time has reduced the number of cases in which they may be required. However, by lowering the dosage requirement of the blocking agent chlorothiazide permits one to obtain a sizeable reduction of blood pressure with fewer side effects of ganglionic blockade. Of the various preparations available, chlorisondamine (Ecolid), mecamyalmine (Inversine) and pentolinium tartrate (Ansolysen) seem to be about equally effective. The important practical points in regard to administering these agents are as follows:

1. Use them in combination with chlorothiazide.
2. Adjust dosage by titration following the blood pressure *frequently*, as you would adjust insulin in a diabetic by following the urine sugars.
3. Have blood pressures recorded in the home by the patient or a member of his family each morning and night.
4. Adjust dosage on basis of blood pressure in the erect position (postural effect).
5. Prevent constipation by administering laxatives freely at bedtime, and if necessary neostigmine (Prostigmine) on awakening in the morning in oral dosages of 15 to 30 mg.

Little more need be said about the ganglionic blocking agents despite their great importance in the treatment of severe hypertension, since the purpose of this paper is to emphasize, primarily, the management of early hypertension. In these less resistant patients they may not be required, or, if required, the dosages can be kept fairly low, making them easier to use, providing one observes the precautions mentioned above.

HOME RECORDINGS OF BLOOD PRESSURE

It is necessary to emphasize the point about home blood pressures. Many hypertensive patients exhibit falsely high pressures in the doctor's office

Antihypertensive agents primarily effect basal blood pressure and are not as effective in combatting the transient pressor responses produces by apprehension. Reliance on falsely high office pressures leads to overdosage and resultant severe side effects. To use the antihypertensive agents effectively a record of day to day and diurnal fluctuations of basal blood pressure is essential.

Many physicians fear the adverse psychological effects of home pressure recordings. But we and others who have utilized this method have not found that the frequent recording of blood pressures disturbs the average patient any more than it disturbs a diabetic to check his urine for sugar. If under treatment you seem to be making no progress with your patient on the basis of office blood pressures there is no reason why you should not take advantage of the more reliable data that home pressures can afford.

PROGRAM FOR MANAGING EARLY HYPERTENSION

The following represents a simple program which should produce significant reduction of blood pressure in the majority of cases of less advanced hypertension. It is aimed at the prevention of organic damage in early asymptomatic patients. To begin with, the patient should buy, or if he cannot afford it, can be loaned a blood pressure apparatus to make a record at home of pressures taken before and after work for one or two weeks prior to any therapy. Then, salt should be restricted moderately and chlorothiazide 500 mg. administered on arising and at bedtime for another one or two weeks. If the blood pressure is not adequately controlled hydralazine (Apresoline), is added 25 mg. three times daily on arising, at 2:00 P.M. and at bedtime for one week and if necessary it can be increased to 50 mg. per dose. If the blood pressure still is not controlled adequately reserpine 0.5 mg. daily is added reducing after two weeks to 0.1 to 0.25 mg. daily at bedtime. If successful, and after several months, one may attempt a gradual withdrawal of all medications except chlorothiazide, withdrawing reserpine first, and if the blood pressure does not rise withdrawing hydralazine. It often is possible in the earlier cases to maintain a reduction with less medication than was necessary originally to obtain the reduction.

If all the measures described above fail to lower the home blood pressure level, either Inversine in a dose of 1.25 mg. after breakfast, at 2:00 P.M. and at bedtime, or Ecolid 10 mg. or Ansolysen 10 mg. may be tried. While this is being done, chlorothiazide and maintainance dosage of reserpine should be maintained. The dosage of the ganglionic agent may then be raised by gradual increments until the blood pressure falls or side effects become troublesome. If the latter occurs, refer the patient to a physician who specializes in the treatment of complicated hypertensive patients. However, this should seldom be necessary. If the blood pressure is controlled, it often is possible to gradually reduce and then discontinue the blocking drug after four to eight months, substituting hydralazine again. Apparently, the early cases often become easier to manage after a prolonged period of blood pressure control.

As patients become older or more advanced along the road of organic damage, less can be achieved and the patients are more difficult to manage. The aged patient with advanced arteriosclerosis and primarily systolic hypertension probably should not be treated vigorously. Also, the very severe cases with fixed high levels of diastolic pressure and extensive renal damage may be beyond help. It seems probably that the pitiful cases of accelerated hypertension need rarely occur if the family physicians institute adequate treatment while the patients are still in the benign phase.

CONCLUSIONS

The advent in the last six years of a series of antihypertensive agents for controlling elevated blood pressure has altered our approach to the management of essential hypertension. As more effective and better tolerated agents have appeared, the opportunity has presented itself of treating early, benign, hypertension more definitively than we could in the past. This places a new responsibility in the hands of the family physician who first sees such patients. For those who take the trouble to apply the simple techniques required, the rewards and satisfactions can be extremely gratifying.

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